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Case Report

A Case of Occult Ectopic ACTH syndrome Treated with Octreotide

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Abstract

It has been reported that in 19% of patients with ectopic ACTH syndrome, a tumor cannot be identified, despite extensive evaluation. We present a case of a 68-year-old woman admitted to our hospital for examination of moon facies, central obesity, hyperpigmentation, bilateral pretibial edema, hypokalemia and hypertension. Both adrenocorticotropin (ACTH) and cortisol levels were elevated with no circadian rhythm. Administration of corticotropin-releasing hormone (CRH) did not change ACTH and only stimulated serum cortisol to less than 10% of basal values. There was no overnight suppression of cortisol in either the low-dose (0.5 mg) or high-dose (8 mg) dexamethasone (Dex) suppression test, and we diagnosed her with ectopic ACTH syndrome, although she rejected an inferior petrosal sinus sampling. The ACTH-producing tumor, however, could not be detected by various imaging modalities, including ^{68}Ga-1,4,7,19-tetraazacyclododecane-NI,NII,NIII,NIIII-tetraaceticacid-(D)-Phe1-Tyr3-octreotide (DOTATOC)-PET CT. Therefore, the patient required treatment with octreotide. After the first treatment, and even after complete remission and relapse, there was overnight suppression of cortisol on the low-dose Dex suppression test, and octreotide resulted in marked improvement of her hypercortisolemia. In the future, we will continue to carefully follow both ACTH and cortisol levels in this rare patient.

Keywords: Ectopic ACTH Syndrome; Octreotide; Somatostatin Receptors

Introduction

Cushing syndrome (CS) was first described by Harvey Cushing in 1932 and results from prolonged exposure to excessive amounts of cortisol production by the adrenal cortex. [1] The main etiologies of CS are divided into 2 types: adrenocorticotropin (ACTH)-dependent and ACTH-independent. In ACTH-dependent CS, there is over-production of ACTH either from a corticotroph pituitary adenoma (Cushing disease) or from ectopic secretion by an extrapituitary tumor, [2] referred to as ectopic ACTH syndrome (EAS). EAS accounts for approximately 15-20% of ACTH-dependent CS, [3] but a tumor could not be identified despite extensive evaluation in 19% of patients with EAS. [4]

Some potentially life-threatening conditions (e.g., acute psychosis, severe hypertension and opportunistic infections) are mainly associated with EAS and require rapid reversal of severe hypercortisolism. If patients with EAS cannot undergo surgery, medical therapies should be applied with inhibitors of adrenocortical steroidogenesis (e.g., ketoconazole, metyrapone and mitotane), a glucocorticoid receptor antagonist (mifepristone), a dopamine agonist (cabergoline) and/or somatostatin (SS) analogues (e.g., octreotide and lanreotide, etc.). [5] The high-affinity SS receptor 2 (SSTR2) has been shown to have the highest binding affinity for octreotide (one of the various SS analogues), which has been known to be useful in the treatment of endocrine tumors. [6] Most patients with EAS express somatostatin receptors, [7] although the utility of octreotide in treating EAS has not yet been well established. [8]

The present report describes the case of a 68-year-old female who displayed occult EAS. A tumor could not be detected by various imaging modalities. Therefore, the patient was given octreotide, which resulted in a marked decrease in both ACTH and cortisol levels after a challenge test. Her hypercortisolemia then dramatically improved.

Case Presentation

The patient was a 68-year-old woman who had been in good health until August 2009, when she consulted her doctor complaining of limb weakness, flushing of the face, facial and leg edema and taste disturbance. Her serum potassium (K) level was markedly decreased and elevation of her blood pressure (BP) was noted. In October, the patient was referred to our hospital for further evaluation. No significant past or family history was elicited. The patient was a non-smoker and non-drinker. On examination, she was 155.0 cm tall and weighed 61.0 kg (body mass index, 25.4 kg/m^2). BP was 165/70 mmHg and pulse was regular at 63 beats/min. Moon facies, central obesity, hyperpigmentation and bilateral pretibial edema were noted, but a buffalo hump and the typical abdominal striae were absent. Laboratory studies were as follows: alanine aminotransferase (ALT) 101 IU/L, lactate dehydrogenase (LD) 392 IU/L, γ-glutamyl transpeptidase (γGTP) 1073 IU/L, fasting plasma glucose (FPG) 199 mg/dL and glycohemoglobin (HbA1c) 8.7% were increased; lymphocytes (lymph) 908/μL, eosinophils (eosin) 29/μL, serum potassium (K) 2.5 mEq/L, albumin (ALB) 3.12 g/dL, and cholinesterase (ChE) 145 IU/L were decreased (Table 1). Endocrinological data at onset are shown in Table 2. ACTH, cortisol and dehydroepiandrosterone sulfate (DHEA-S) levels were increased (209.0 pg/ml, 43.9 μg/dL and 512 μg/dL, respectively). Both ACTH and cortisol were elevated with no circadian rhythm. Administration of corticotropin-releasing hormone (CRH) did not change ACTH and only stimulated serum cortisol to less than 10% of basal values. In the high-dose (8 mg) dexamethasone (Dex) suppression test, there was no overnight suppression of cortisol. Her 24-hour urine cortisol level was elevated. The octreotide suppression test (100 μg subcutaneous injection) resulted in a marked reduction in both ACTH and cortisol levels from 254.0 pg/mL to 95.0 pg/mL and from 96.2 μg/dL to 45.2 μg/dL, respectively with the nadir at 6 hours.

Table 1. Chemical and hematological data.

	At onset	At relapse	Reference range
AST (U/L)	29	20	13-33
ALT (U/L)	101	40	6-27
LDH (U/L)	392	182	119-229
ALP (U/L)	245	133	115-359
γGTP (U/L)	1073	70	10-47
ChE (U/L)	145	194	185-431
ALB (g/dL)	3.12	3.70	3.80-5.70
BUN (mg/dL)	15.6	16.1	8.0-22.0
Cr (mg/dL)	0.54	0.60	0.40-0.70
UA (mg/dL)	2.8	4.0	2.3-7.0
eGFR (mL/min/1.73m^2)	85.7	74.7	90 ≤
Na (mmol/L)	144	146	138-146
Cl (mmol/L)	98	107	99-109
K (mmol/L)	2.5	3.6	3.6-4.9
LDL-C (mg/dL)	102	103	70-139
HDL-C (mg/dL)	35	59	40-80
TG (mg/dL)	138	109	30-149
FPG (mg/dL)	199	101	80-112
HbA1c (%)	8.7	6.1	4.6-6.2
CRP (mg/dL)	0.09	< 0.06	0.00-0.30
Leukocyte (/μL)	7320	6510	3500-8500
Neut (/μL)	6061	5013	2000-7500
Lymph (/μL)	908	684	1500-4000
Mono (/μL)	278	306	200-800
Eosin (/μL)	29	46	40-400
Baso (/μL)	15	20	10-100

AST, aspartate : 2-oxoglutarate aminotransferase; ALT, alanine : 2-oxoglutarate aminotransferase; LDH, lactat dehydrogenase; ALP, alkaline phosphatase; γGTP, γ-glutamyl transpeptidase; ChE, cholinesterase; ALB, albumi BUN, blood urea nitrogen; Cr, creatinine; UA, uric acid; eGFR, estimated glomerular filtration rate; LDL-C, lo density lipoprotein-cholesterol; HDL-C, high density lipoprotein-cholesterol; TG, triglyceride; FPG, fasting plasm glucose; HbA1c, glycohemoglobin; CRP, C-reactive protein; Neut, neutrophil; Lymph, lymphocyte; Mon monocyte; Eosin, eosinophil; Baso, basophil;

Table 2. Endocrinological data and endocrine tests.

At onset						
Circadian rhythm (clock)	6:00		12:00		16:00	
ACTH (pg/mL)	209 [7.2-63.3]		196		198	
Cortisol (μg/dL)	43.9 [4.0-18.3]		49.2		46.5	
DHEA-S 512 μg/dL [12-133]	24-hour Urine cortisol 2030 μg/day [11.2-80.3]					
NSE 5.8 ng/mL [≤ 10]	Serotonin ≤ 0.01 μg/dL [0.04-0.35]					
24-hour Urine 5HIAA 3.6 mg/day [1.0-6.0]			Calcitonin 12 pg/mL [29.7-45.9]			
CRH (100 μg, i.v.) (min)	0	15	30	60	90	120
ACTH (pg/mL)	268	215	200	212	202	203
Cortisol (μg/dL)	84.6		93.0	74.6	81.5	87.2
Dexamethasone suppression test (clock)			8:00		8:00	
ACTH (pg/mL)			252		224	
Cortisol (μg/dL)			89.2		79.0	
Octreotide (100 μg, s.c.) (hour)	0	2	6	8	10	
ACTH (pg/mL)	254	131	95	238	140	
Cortisol (μg/dL)	96.2	70.0	45.2	75.5	62.0	
At relapse						
Circadian rhythm (clock)	6:00		12:00		16:00	
ACTH (pg/mL)	177		147		122	
Cortisol (μg/dL)	32.9		31.1		28.4	
DHEA-S 331 μg/dL	24-hour Urine cortisol 1250 μg/day					
CRH (100 μg, i.v.) (min)	0	15	30	60	90	120
ACTH (pg/mL)	201	187	201	214	215	217
Cortisol (μg/dL)	50.6		47.2	49.7	50.3	48.9
Dexamethasone suppression test (clock)			8:00		8:00	
ACTH (pg/mL)			167		183	
Cortisol (μg/dL)			55.0		56.4	

Dexamethasone (8 mg) was given orally at 23:00 the day before.

Numbers in brackets indicate the reference range.

ACTH, adrenocorticotropin; DHEA-S, dehydroepiandrosterone sulfate; NSE, neuron-specific enol

5-HIAA, 5-hydroxyindoleacetic acid; CRH, corticotropin-releasing hormone

Whole-body computed tomography (CT) revealed bilateral adrenal gland swelling, and a magnetic resonance imaging (MRI) study of her brain found no pituitary adenoma. Plain MRI scan and enhanced spin echo sequence T1WI and T2WI in sagittal, coronal and axial views were performed with a 1.5-Tesla MR scanner. The parameters used were as follows: interlaced scan with scanning field of 180 × 180 mm and layer thickness of 3 mm. Gadolinium-diethylenetriaminepentaacetic acid (Gd-DTPA) was used as a contrast agent. Although the patient rejected inferior petrosal sinus sampling (IPSS), EAS was suspected, based on the above results. CT and MRI, abdominal ultrasound (AUS), ^{99m}Tc bone scintigraphy, ^{68}Ga scintigraphy and even functional imaging procedures such as somatostatin receptor scintigraphy with ^{111}In-octreotide (OctreoScan™, Mallinckrodt, Ireland) (Figure 1) and ^{18}F-fluorodeoxyglucose-positron emission tomography (FDG-PET) (Figure 2A) failed to localize the source of ectopic ACTH production. However, it was necessary to quickly lower the patient's serum cortisol the because the CT scan revealed bilateral adrenal gland swelling, right lower lobe pneumonia and mesenteric panniculitis of the transverse colon, and MRI detected 11th and 12th thoracic vertebral compression fractures. Therefore, the patient was given octreotide twice daily subcutaneous injection (100 μg/day) in January 2010 because of a dramatic reduction in both ACTH and cortisol during the octreotide suppression test as well as liver dysfunction. After octreotide administration, ACTH and cortisol levels decreased to within normal range for 5 days (Figure 3). Furthermore, serum K normalized for eight days (data not shown). Her symptoms and the findings on CT (pneumonia and mesenteric panniculitis of the transverse colon) dramatically improved. In February 2010, octreotide was changed to long-acting depot octreotide acetate (Sandostatin® LAR), 20 mg every 4 weeks. During the clinical course, her symptoms disappeared and changes in ACTH, cortisol and serum K levels remained within normal range. Then, Sandostatin LAR was reduced to 10 mg every 4 weeks in December 2010 (Figure 3). Furthermore, per the wishes of the patient, Sandostatin LAR was discontinued in January 2011 (Figure 3). Unexpectedly, there was an overnight suppression of cortisol with the low-dose (0.5 mg) Dex suppression test. From this result, we thought the ACTH had been secreted from the patient's pituitary gland rather than from an unknown origin after discontinuation of Sandostatin LAR.

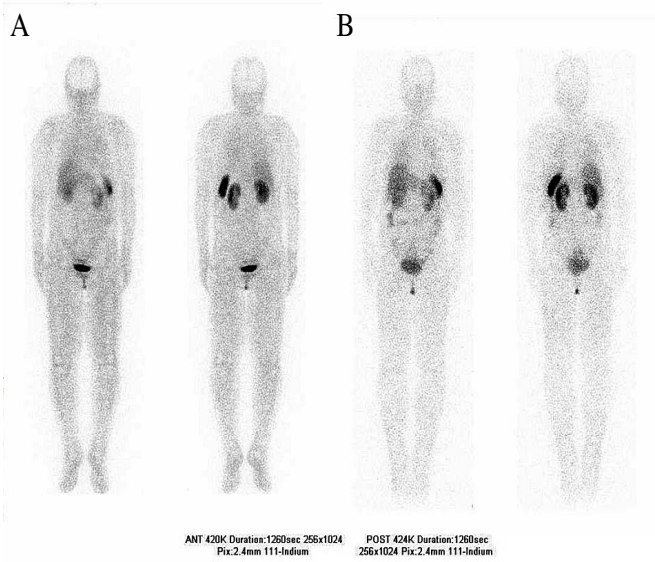

Figure 1. Whole-body coronal view of somatostatin receptor scintigraphy using ^{111}In-octreotide (A) Image at 4 hours and (B) at 24 hours after injection of ^{111}In-octreotide.

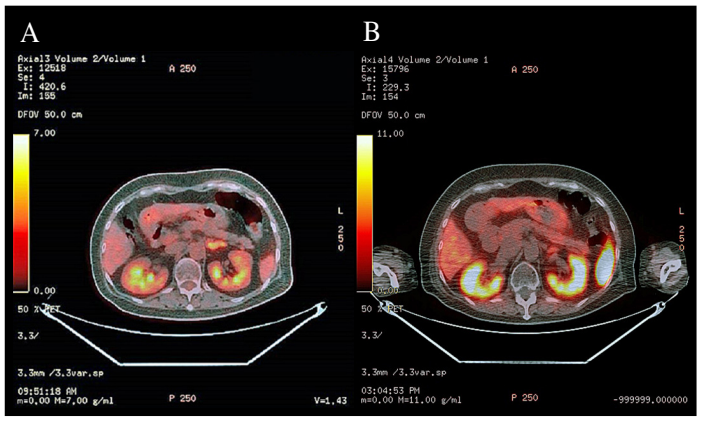

Figure 2. Horizontal view of (A) [18F] fluorodeoxyglucose-positron emission tomography (FDG-PET) and (B) 68Ga-1,4,7,19-tetraazacyclododecane-NI,NII,NIII,NIIII-tetraaceticacid-(D)-Phe1-Tyr3-octreotide (DOTATOC)-PET computed tomography (CT).

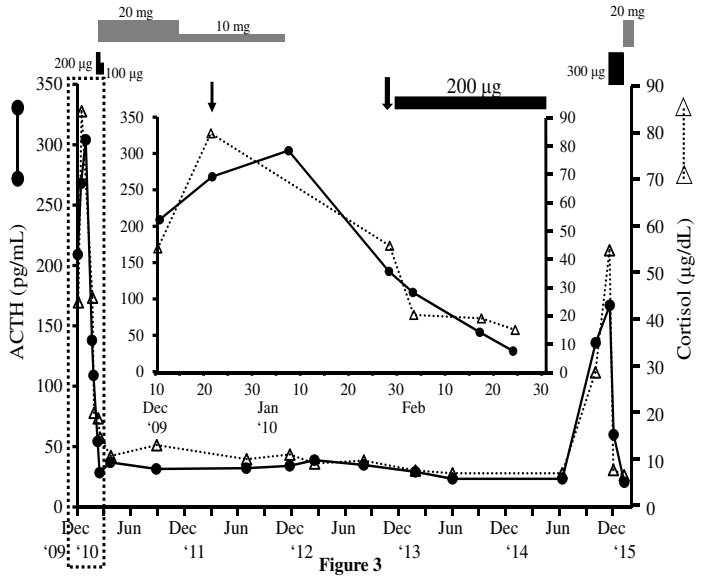

Figure 3. Clinical course of patient with rare occult ectopic ACTH syndrome Changes in ACTH (•) and cortisol (Δ) levels are shown. Graph located in the center is obtained by expanding the portion in the dashed square; black box shows treatment with octreotide; gray box shows treatment with long-acting depot octreotide acetate (Sandostatin® LAR); thin arrow shows octreotide challenge test; thick arrow shows scintigra.

Whole-body CT was repeated at 12-month intervals. Then, it was followed by 3.8 years of remission. In October 2014, a recurrence of over-production of ACTH from an ectopic tumor was suspected (Figure 3). ALT 40 IU/L and γ-GTP 70 IU/L were increased; lymphs 684/μL, serum K 3.6 mEq/L, ALB 3.70 g/dL were all decreased (Table 1). Endocrinological data at the time of relapse are shown in Table 2. Both ACTH and cortisol were elevated with no circadian rhythm and 24-hour urine cortisol excretion was elevated at 2500 μg/day. A high-dose (8-mg) Dex suppression test did not reveal any suppression of baseline ACTH or cortisol levels (ACTH 183 pg/mL, cortisol 56.4 μg/dL). On October 15, 68Ga-1,4,7,19-tetraazacyclododecane-NI,NII,NIII,NIIII-tetraaceticacid-(D)-Phe1-Tyr3-octreotide (DOTATOC)-PET CT was performed but did not display any abnormal uptake (Figure 2B). Therefore, she was given octreotide once more. After octreotide administration, ACTH, cortisol and serum K levels remarkably decreased to almost within normal range for 12 days (59.9 pg/mL, 8.2 μg/dL and 4.8 mEq/L respectively) (Figure 3). Her symptoms also improved. At present, we are observing her clinical course with administration of Sandostatin LAR (20 mg every 4 weeks) in place of octreotide.

Discussion

It has been reported that EAS accounts for about 10-20% of all cases of Cushing syndrome. [9] Alexandraki et al. reported that the source of ACTH remains unidentified in approximately 12-37.5% of patients with EAS. [10]

A definitive diagnosis in our case remains unclear due to the patient's refusal of IPSS and our not using half-dose contrast material for the dynamic 3-Tesla MRI. [11] The markedly elevated ACTH and cortisol levels with severe hypokalemia and the lack of stimulation of them upon CRH administration as well as the result of the high-dose Dex suppression test, however, suggest a diagnosis of EAS. We considered that a marked reduction in both ACTH and cortisol levels by the octreotide suppression test also indicated a diagnosis of EAS rather than CD because Díez et al. have expressed the hypothesis that octreotide does not inhibit ACTH levels in patients with CD *in vivo*, suggesting that cortisol might exert SSTR down-regulation *in vivo*. [8]

In our case, the ACTH source could not be identified by any imaging modalities such as CT, MRI, AUS, 99mTc bone scintigraphy, 68Ga scintigraphy, OctreoScan™ (Figure 1), FDG-PET (Figure 2A) or 68Ga-DOTATOC-PET CT (Figure 2B). It has been reported that the incidence of patients with CS caused by nonmalignant disease and carcinoid is approximately 2.4 cases/million/year. [12] Therefore, occult EAS is exceedingly rare (incidence is speculated to be less than 0.2 cases/million/year).

Neuroendocrine tumors (NETs) that cause EAS have often been known to express SSTR. SS analogues labeled with gamma-emitting radionuclides are able to image SSTR-expressing tumors on scintigraphy. The sensitivity of 68Ga-DOTATOC-PET CT in patient-based studies is 92-100% and the specificity is 83-100%. [13] 68Ga-DOTATOC-PET CT has been reported to be superior to FDG-PET in the detection of NETs, [14] and the affinity in binding SSTR2 was higher than that of OctreoScan™ (2.5±0.5 nM vs 22±3.6 nM). [15] It has been demonstrated that 68Ga-DOTATOC-PET CT was more efficient than OctreoScan™ single-photon emission CT in the detection of small NETs. [16]

In our case, we could not detect the origin of EAS, even with ^{68}Ga-DOTATOC-PET CT, although the effect of the octreotide was sustained, in spite of the common occurrence of treatment escapes.

Potential mechanisms include: (1) a decrease in the number and/or affinity of SSTRs, (2) a decrease in responsiveness due to receptor uncoupling from second messenger activation, (3) an outgrowth of SSTR-negative cell clones, (4) a reduction of SSTR by cortisol, and (5) antibodies to octreotide, etc. [17, 18] Gilardi et al. reported 5 cases of ectopic ACTH-producing tumors which were between 5.8 and 7.4 mm in diameter. [19] The size of the lesion producing ACTH in our patient is presumed to be below the detection limit of ^{68}Ga-DOTATOC-PET CT testing or other modalities.

Interestingly, there was an overnight suppression of cortisol on the low-dose (0.5 mg) Dex suppression test during remission. At that point, it was considered that our patient's ACTH was from pituitary gland secretion rather than from the previously suspected unknown ectopic origin, although we found it perplexing that no symptoms of adrenal dysfunction occurred. Lightman et al. have shown *in vivo* that octreotide does not inhibit ACTH secretion in normal subjects. [20] Therefore, we speculated that secretion of ACTH from the patient's normal pituitary gland recovered over time with a gradual decreasing of ACTH from the ectopic tumor as a result of octreotide suppression. Perhaps that represented a complete remission of EAS as a result of treatment with octreotide, but we also speculated our case might be cyclic Cushing syndrome (CCS) because both ACTH and cortisol had already shown a downward trend after the first administration of octreotide. That is, the possibility of spontaneous remission could not be excluded. In patients with CCS, it has been reported that a prevalence of 26% of EAS and 12% of CCS have had an occult source of ACTH. [21] Pathophysiologically, CCS has been proposed to result from either the occurrence of spontaneous, episodic hemorrhage in the tumor resulting in temporary damage of actively ACTH-secreting tumor cells or from the synchronic growth and death of them, which may lead to periodic hypercortisolism. [22] Another mechanism has been suggested, i.e., the existence of negative feedback control of ACTH production by an unknown origin of cortisol secretion. [23] However, because the second treatment with octreotide was also effective, we have speculated that our patient did not have CCS.

In conclusion, we report herein a rare case of the occult ectopic ACTH syndrome treated with octreotide. We could not detect the origin of EAS, even with ^{68}Ga-DOTATOC-PET, although the effect of octreotide was sustained. In the future, we will carefully follow this patient's ACTH and cortisol levels and clinical course.

Conflicts of Interest

The authors declare that there are no conflicts of interest regarding the publication of this paper.

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